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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,669	10/01/2003	David Botstein	10466/485	1088

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,669	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are cancelled.

Claim 22 has been amended.

2. Claims 22-26 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Correction of Inventorship

The request to correct the inventorship, pursuant to 37 C.F.R. § 1.48(b) deleting inventors Kevin P. Baker, Dan L. Eaton, Napoleone Ferrara, Ellen Filvaroff, Mary E, Gerristen, Ivar J. Kljavin, Mary A. Napier and Daniel Tumas has been accepted. Therefore, the inventorship of the present application has been corrected to David Bostein, Audrey Goddard, Paul J. Godowski, J. Christopher Grimaldi, Austin L. Gurney, Kenneth J. Hillan, Margaret Ann Roy and William I. Wood.

Withdrawn Objections/rejections

4. The objections to the specification as lacking a priority claim on the first line of the specification, as containing embedded hyperlinks and for the use of trademarks are withdrawn in view of the amendments to the specification.

5. The objection to the Oath/Declaration as containing non-initialed, non-dated changes to the citizenship of inventor Dan L. Eaton is withdrawn in view of the correction of inventorship, deleting Dan L. Eaton as an inventor.

6. The rejection of claims 22-26 under 35 U.S.C. 112, second paragraph as being indefinite in the recitation "diagnosing said subject with cancer" in claim 22 is withdrawn in view of the amendments to the claim.

Response to Arguments

7. The objection to the title of the invention as not being clearly indicative of the invention to which the claims are directed is maintained.

The response filed 6/5/2006 does not address this objection and thus, the objection is maintained.

8. The rejection of claims 22-26 under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility is maintained.

Applicant disagrees that one of skill in the art would find it more likely than not that the PRO357 polypeptide is totally uncharacterized. Applicant refers to the sequence of the PRO357 polypeptide and several features of the sequence that were apparently predicted from the sequence. However, no information is provided in the gene amplification data regarding level of expression, activity, or role in cancer of the PRO357 polypeptide. Further, the examiner acknowledges applicants remarks regarding the use of framework markers to control for aneuploidy, however, even assuming that the PRO357 polynucleotide is amplified in cancer, this does not provide a specific benefit in currently available

form for the presently claimed PRO357 polypeptide and antibodies thereto in a manner sufficient to satisfy the utility requirements of 35 U.S.C. § 101.

Applicants' argue that based on the Goddard declaration one of ordinary skill in the art would find it credible that the claimed PRO357 polypeptides have utility. Applicants' arguments have been fully considered but they are not persuasive. The declaration is limited to a discussion regarding the significance of gene amplification and is not directed to a correlation between PRO357 polynucleotide amplification and PRO357 polypeptide expression. The examiner is not arguing that an increase in gene copy number is not significant and useful. The examiner is arguing that the present specification fails to disclose the correlation between PRO357 polynucleotide amplification and PRO357 polypeptide expression or the significance of any such correlation.

Applicants' argue that the Polakis declaration shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants' arguments have been fully considered but they are not persuasive. The specification provides no information regarding increased PRO357 mRNA levels in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-26 based upon 35 U.S.C. §§ 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and protein levels, and not gene amplification levels and protein levels.

The examiner acknowledges the additional evidence submitted by applicant, including the art of Pollack, Ornoft, Hyman, Bermont, Varis, Hu,

Papotti, Walmer, Janssens, Hahnel, Kammori, Bea, Maruyama and Futcher and applicants' arguments therewith as well as applicants' response to the art cited by the examiner in the previous Office Action. However, the examiner will focus on the relevant issues and evidence as they pertain to the utility of the PRO357 polypeptide and its expression in lung and colon cancer to which the claimed diagnostic method is directed.

Applicants argue that the examiner has not met the evidentiary burden because the examiner must show that it is more likely than not that a correlation, in general, does not exist. Applicant's arguments have been fully considered but they are not persuasive. The M.P.E.P. reminds Office personnel that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. The examiner has cited Konopka (reference W on PTO-892 mailed 2/27/2006) and Pennica (reference V on PTO-892 mailed 2/27/2006) as countervailing evidence that that the utilities asserted for the PRO357 polypeptide are not substantial because a specific benefit does not exists in currently available form. A specific benefit does not exists in currently available form because the skilled artisan would not know if the expression of the PRO357 polypeptide would be upregulated, down-regulated, or unchanged in lung or colon cancer. Therefore, amplification of the PRO357 polynucleotide does not impute a specific, substantial, and credible utility to the PRO357 polypeptide. The examiner has provided the art of Konopka and Pennica (PTO-892 mailed

2/27/2006) as evidence that the gene amplification data does not impute a specific, substantial, and credible utility to the PRO357 polypeptide. In the absence of any evidence to the contrary, the examiner has accordingly provided countervailing evidence that shows that one of ordinary skill in the art would have a legitimate basis to doubt the utility of the PRO357 polypeptide and antibodies thereto.

It is acknowledged that, in general, FISH and HIC results with HER-2/neu correlate well. However, discordant results are seen and the significance of these results is unclear. Hanna (cited by Applicants), first page, right column, last paragraph. Therefore, Hanna supports the examiner's position that the gene amplification data does not impute a specific, substantial, and credible utility to the PRO357 polypeptide and antibodies thereto.

Appellants argue that Pennica and Konopka do not suffice to make a prima facie case that it is more likely than not that no generalized correlation exist between gene amplification and increased polypeptide levels because Pennica and Konopka are not directed to genes in general but to a single gene or genes within a gene family. Pennica and Konopka provide evidence that the skilled artisan cannot assume that any one gene's amplification results in mRNA and polypeptide overexpression. The issue at hand also concerns only one gene and the protein it encodes. Applicants have not provided any testing of the role, activity, or expression of the PRO357 polypeptide in cancer.

The examiner also rejects Applicants' argument that the teachings of Pennica are specific to WISP genes and that Pennica has no teaching regarding

correlation of gene amplification and protein expression in general. Pennica is evidence that not all gene amplifications are associated with overexpression of the corresponding gene product and that the skilled artisan would not have appreciated that PRO357 gene amplification, without more, would have suggested a specific and substantial patentable utility for the PRO357 polypeptide and antibodies thereto. The examiner is not arguing that a correlation between PRO357 polynucleotide amplification and PRO357 polypeptide expression does not exist. The examiner is arguing that the present specification fails to disclose what that correlation is or the significance of any such correlation.

If one is to argue, as Applicants have done, that "it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon," then one would also have to accept the argument that the apparent amplification observed in the present application for the PRO357 polynucleotide may be caused by another gene in its amplicon, which would force the examiner to conclude that the present application's gene amplification data fails to satisfy the utility requirements of 35 U.S.C. § 101 for the PRO357 polypeptide *and* PRO357 polynucleotide.

Applicants argue that even if a prima facie case had been established, that it should be withdrawn because simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the protein is not over-expressed, leading to better determination of a suitable therapy, and absence of protein over-expression is crucial information

because a clinician will decide not to treat a patient with agents that target the gene product, thereby saving money and unnecessary treatment, as evidenced by Hanna. Applicants argue that diagnosis of breast cancer includes testing both HER-2/neu gene amplification and HER-2/neu protein expression, and that an assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment. Applicant's arguments have been fully considered but they are not persuasive. Applicants are apparently basing their conclusions on Hanna at the first page, right column, last paragraph. The examiner does not agree with Applicants' interpretation of Hanna. Hanna clearly states that the clinical significance of the discordant results is unclear. Hanna states that HER-2/neu testing will utilize IHC as a screen, followed by FISH in IHC-negative cases, presumably to better understand the significance of these discordant results. This teaching does not provide a specific benefit in currently available form for the presently claimed PRO357 polypeptide and antibodies thereto. Based on the disclosure one of skill in the art would be required to perform further testing to determine the expression level of the PRO357 polypeptide, its correlation to the disclosed PRO357 polynucleotide, if any, and determine whether PRO357 polypeptide levels are specific to lung and colon cancer, consistent and measurable in order to practice the claimed invention. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. A strong probability of utility is not sufficient to establish practical utility; *Wu v. Jucker*, 167 USPQ 467, 472 (Bd. Pat. Inter. 1968) (screening test where there

was an indication of possible utility is insufficient to establish practical utility)". A practical utility is a shorthand way of attributing "real-world" value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner, which provides some immediate benefit to the public.

Rather than setting a de minimis standard, § 101 requires a utility that is "substantial", i.e., one that provides a specific benefit in currently available form. The examiner accepts for argument's sake that a person skilled in the art could derive some data regarding PRO357 polypeptide expression in tumors in which the PRO357 polynucleotide is amplified. The examiner can also accept, for argument's sake, that such data could be used to correlate PRO357 polypeptide expression with PRO357 polynucleotide amplification. However, the specification provides no guidance to enable the skilled artisan to use data relating to PRO357 polypeptide expression in any practical way. The specification simply provides no guidance regarding what the PRO357 polypeptide-specific information derived from such data would mean. Assume, for example, that a researcher observed that PRO357 polypeptide expression was altered with respect to tissues in which the PRO357 polynucleotide was not amplified. The specification provides no basis on which a skilled worker would be able to determine whether that result is meaningful. Maybe the meaning in a change in PRO357 polypeptide expression would depend on other factors, but again the specification provides no hint what other factors might be important. The specification simply provides no guidance as to how to interpret the results that might be seen using PRO357 polypeptide expression. In effect, Applicants'

position is that the claimed PRO357 polypeptides and antibodies thereto are useful because those of skill in the art could experiment with them and figure out for themselves what any observed experimental results might mean. The examiner does not agree that such a disclosure provides a "specific benefit in currently available form."

For these reasons the rejection of claims 22-26 under 35 U.S.C. § 101 is deemed proper and is maintained.

9. The rejection of claims 22-26 under 35 U.S.C. 112, first paragraph, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant argues as above that the claimed invention is adequately supported by an asserted utility that is both specific and substantial. Applicants' arguments have been fully considered but they are not persuasive. As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101.

Conclusion

10. No claims are allowable.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

SHEELA HUFF
PRIMARY EXAMINER